REMARKS/ARGUMENTS

Applicants acknowledge, and wish to thank the Examiner for, the withdrawal of the rejections of the claims under Section 112, first and second paragraphs, that were set forth in the previous Office Action. Applicants also wish to thank the Examiner for the helpful advice provided during the informal telephone interview conducted with Applicants' representative on November 17, 2005, wherein the pending claims were discussed. The Examiner's suggestions have been taken into account in preparing this response.

Claims 25 and 39 have been canceled without prejudice to or disclaimer of the subject matter contained therein, and claims 20-24, 31, 34, 35, and 38 have been amended as noted herein below. No new matter is added by way of claim amendment.

In keeping with the Examiner's suggestion, all claims previously reciting a dosage range of IL-2 or variant thereof that included the term "about" (i.e., claims 20, 21, 22, 31, 34) have been amended to remove this term from the range. Furthermore, independent claim 20 has been amended to recite "3 mIU/m^2 to 14 mIU/m^2" as the dosage range for IL-2 or variant thereof, and to require that the IL-2 or variant thereof is administered subcutaneously. Support for these amendments resides, for example, in original claim 22, wherein 3 mIU/m^2 is identified as a preferred lower end of the dosage range for IL-2 or variant thereof, and original claim 25, wherein subcutaneous administration of the IL-2 or variant thereof was recited. Accordingly, dependent claim 21 has been amended to recite "3 mIU/m^2 to 12 mIU/m^2" as the dosage range for IL-2 or variant thereof. Dependent claim 23 has been amended to recite a dose of IL-2 or variant thereof of about 3.5 mIU/m^2; support for this amendment resides in the specification, for example, at page 12, line 1. Dependent claim 31 has been rewritten in independent form to include limitations of the respective base claims. This claim now recites "3 mIU/m^2 to 14 mIU/m^2" as the dosage range for IL-2 or variant thereof and requires that the IL-2 or variant thereof is administered subcutaneously. Support for these amendments resides, for example, in original claims 22 and 34, wherein 3 mIU/m^2 is identified as a preferred lower end of the dosage range for IL-2 or variant thereof, and original claim 39, wherein subcutaneous administration of the IL-2 or variant thereof was recited. Dependent claim 35 has been amended to recite a dose of IL-2 or variant thereof of about 3.5 mIU/m^2; support for this amendment resides in the

specification, as noted above. Claims 24, 34, and 38 have been amended to correct an obvious typographical error.

These claim amendments were not presented earlier as Applicants earnestly believed that the previously presented claims recited patentable subject matter. The Examiner is respectfully requested to enter these claim amendments to further prosecution or to place the application in better condition for appeal.

Claims 20-24, 26-38, and 40-44 are now pending in this application. Reconsideration of the claims is respectfully requested in view of the foregoing amendments and following remarks. The Examiner's comments in the outstanding Office Action are addressed below in the order set forth therein.

The Rejection of the Claims Under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 20-44 stand rejected under 35 U.S.C. §103(a) in view of Grillo-López, U.S. Patent No. 6,455,043 (hereinafter, the "'043 patent") or WO 00/09160, the corresponding international patent application publication, in view of Applicants' admission on page 18, line 11, continuing through page 21, where variants of IL-2 known in the art are disclosed. Claims 25 and 39 have been canceled. This rejection is respectfully traversed as applied to the remaining claims.

Independent claim 20 is directed to a method of treating non-Hodgkin's lymphoma in a subject, where the method comprises administering to the subject at least one therapeutically effective dose of an anti-CD20 antibody or fragment thereof in combination with subcutaneous administration of at least one therapeutically effective dose of IL-2 or variant thereof. The therapeutically effective dose of anti-CD20 antibody or fragment thereof is in the range from about 125 mg/m^2 to about 500 mg/m^2, and the therapeutically effective dose of IL-2 or variant thereof is in the range from 3 mIU/m^2 to 14 mIU/m^2. Independent claim 31 is directed to a method of treating non-Hodgkin's lymphoma in a subject, where the method comprises administering at least one therapeutically effective dose of an anti-CD20 antibody or fragment thereof to said subject beginning on day 1 of a treatment period followed by subcutaneous administration of at least one therapeutically effective dose of interleukin-2 (IL-2) or variant

thereof to said subject within 7 days. The therapeutically effective dose of anti-CD20 antibody or fragment thereof is in the range from about 125 mg/m^2 to about 500 mg/m^2, and the therapeutically effective dose of IL-2 or variant thereof is in the range from 3 mIU/m^2 to 14 mIU/m^2.

Claims 20-24 and 26-30 thus recite methods of treating non-Hodgkin's lymphoma that comprise administering subcutaneously at least one therapeutically effective dose of IL-2 or variant thereof in the range from 3 mIU/m^2 to 14 mIU/m^2 *in combination* with the administration of at least one therapeutically effective dose of anti-CD20 antibody or fragment thereof. Applicants respectfully submit that the '043 patent and corresponding WO 00/09160 publication fail to provide the requisite guidance as to how to modify the IL-2 doses disclosed in these cited references, which are disclosed solely *for use in single-agent therapy*, to arrive at the presently claimed dosing range for IL-2 or variant thereof that is *to be used in combination* with anti-CD20 antibody therapy. The Examiner notes that the IL-2 doses disclosed in these two cited references include 2 mIU/m^2, wherein the '043 patent cites to Lauria *et al.*, and 0.45 mIU/m^2, where the '043 patent cites to Caliguiri *et al.* See the Office Action mailed June 17, 2005, at page 4. The Examiner submits that the effectiveness of these low IL-2 doses as taught by the prior art would have led one of skill in the art to use these low IL-2 doses in combination therapy, thus rendering Applicants' invention obvious. Applicants respectfully disagree.

At most, the teachings of the '043 patent and its companion WO publication suggest that a Phase I trial is being performed to investigate the safety and potential efficacy of IL-2/anti-CD20 combination therapy in autologous bone marrow transplant recipients (see, for example, the '043 patent at col. 15, lines 25-28), and that a Phase II trial is being performed to evaluate the efficacy and the incidence of HACA formation in patients with low-grade, follicular B-cell, or mantle cell lymphoma receiving low-dose IL-2 and the anti-CD20 antibody Rituxan® (see, for example, the '043 patent at col. 15, lines 29-36). The doses of IL-2 and anti-CD20 antibody to be used in these alleged clinical trials are not disclosed. Nor do these two cited references suggest IL-2 dose ranges suitable for use in combination therapy with IL-2 and anti-CD20 antibody. Even if one of skill in the art were motivated to continue with the "combination anti-

CD20 antibody/IL-2 therapy" disclosed in the '043 patent and its companion WO publication, the guidance provided in these two cited references is merely an invitation to experiment.

Yet an invitation to experiment is not sufficient grounds to reject an invention as obvious. It is well settled in the case law that in order to render a claimed invention obvious within the meaning of 103, the prior art must contain some suggestion of the desirability and the manner of making the proposed modification. See, e.g., *In re Antonie*, 559 F.2d 618, 195 USPQ 6; *In re Taborski*, 183 USPQ 50; and *In re Murch,* 175 USPQ 89. Moreover, the mere fact that the prior art could be modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. *In re Laekowski*, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989).

The '043 patent and companion WO publication do not guide the skilled artisan to the recited dosage range of IL-2 or variant thereof that Applicants have discovered is beneficial in combination with anti-CD20 antibody to treat non-Hodgkin's lymphoma. Rather, at most these two references teach that the very low doses of IL-2 relied on for this rejection (i.e., 2 mIU/m^2 and 0.45 mIU/m^2) were efficacious for cancer treatment when administered in *single-agent* therapy. No guidance is provided as to how these low IL-2 doses should be modified for combination therapy with an anti-CD20 antibody to safely and efficaciously treat non-Hodgkin's lymphoma. The low doses of IL-2 taught by the '043 patent and companion WO publication were not predictive of the higher IL-2 doses that Applicants' have discovered are efficacious in treatment of non-Hodgkin's lymphoma when administered subcutaneously in combination with an anti-CD20 antibody therapy.

Furthermore, the specific dosing regimen recited in independent claim 31 and claims dependent therefrom is not suggested by these two cited references. The '043 patent and its companion WO publication provide no guidance whatsoever as to a dosing regimen to be used for combination therapy with IL-2 and anti-CD20 antibody. In the absence of such guidance, one of skill in the art is left with a myriad of possible dosing regimens to choose from, with no reasonable expectation of successfully modifying the teachings of the '043 patent and WO 00/09160 publication to arrive at Applicants' claimed invention. Again, this is at most an

invitation to experiment, yet an invitation to experiment is not sufficient grounds to reject an invention as obvious.

Applicants' have discovered what was not taught or suggested by these two cited references, that IL-2 administered subcutaneously to non-Hodgkin's lymphoma patients within the claimed dosage range of 3 mIU/m^2 to 14 mIU/m^2 provides for efficacy of treatment with IL-2/anti-CD20 antibody therapy. Further, Applicants have discovered that IL-2 administration frequency can advantageously be decreased from daily to thrice-weekly dosing to provide for superior therapeutic results with IL-2/anti-CD20 antibody therapy in these patients. See the results of the phase I studies related to the present invention and published as Gluck *et al.* (2004) *Clinical Cancer Research* 10:2253-2264 (submitted herewith as Exhibit A), and which are summarized in Hurst *et al.*, 2002 American Society of Clinical Oncology Annual Meeting, Abstract 1131 (poster and summary abstract submitted herewith as Exhibit B). These studies revealed that all responders to combination IL-2 anti-CD20 antibody therapy were seen in treatment cohorts receiving total weekly IL-2 doses of at least 30 MIU (approximately 17.6 mIU/m^2 based on a conversion factor that an average person has a body surface area of approximately 1.7 m^2). Note that the daily subcutaneous administration protocol required a daily dose of IL-2 above 4.5 MIU (i.e., above approximately 2.6 mIU/m^2), and thus a total weekly IL-2 dose above 30 MIU, to obtain a beneficial response beyond stable disease (SD). However, complete responses (CR) could be obtained when an equivalent total weekly IL-2 dose of 30 MIU was administered by a thrice-weekly dosing schedule wherein 10 MIU (i.e., approximately 5.9 mIU/m^2) IL-2 was administered at each dose. Thrice-weekly IL-2 dosing during combination therapy with anti-CD20 antibody was not only better tolerated than the daily IL-2 dosing but was also associated with more tumor responses. The majority of these responders fell within the treatment cohort receiving 10 MIU IL-2 thrice-weekly in combination with the anti-CD20 antibody dosing. Applicants respectfully submit that these efficacious IL-2 doses and the superior efficacy of the thrice-weekly IL-2 dosing protocol could not have been predicted from the teachings of the '043 patent and its companion WO publication.

As previously made of record, the fact that variants of IL-2 were known in the art at the time of Applicants' invention does not provide any suggestion as to what doses of anti-CD20

antibody or fragment thereof and IL-2 or variant thereof should be used *in combination* to treat human subjects with non-Hodgkin's B-cell lymphomas, nor does it provide guidance as to dosing regimens to be used. This missing information is not taught or suggested in the cited '043 patent or WO 00/09160 publication.

The Examiner maintains this obviousness rejection in view of the IL-2+Rituxan® clinical trials referred to in the '043 patent and corresponding WO publication. Applicants respectfully stand by their assertion that there is sufficient evidence of record to bring into question whether these clinical trial trials were ever conducted, or, if they were conducted, whether safe and efficacious results were actually obtained. Applicants again point to the 2003 review article by Grillo-López, a copy of which is resubmitted concurrently herewith as Exhibit C in view of the Examiner's indication that the previously submitted copy could not be found. In this review article, the author refers to use of IL-2 in combination with Rituxan® *only in the context of future avenues of research*, stating "Other promising rituximab combinations include interleukin-2, granulocyte-macrophage colony-stimulating factor, alemtuzumab . . . and epratuzumab" (page 772, col. 2, first full paragraph, lines 5-9). However, Grillo-López provides no indication that he is aware of any such trial being underway with the IL-2+Rituxan® combination. Yet, as an inventor of the '043 patent, Grillo-López most assuredly was in a position at the time of writing this review article to either provide preliminary or definitive results of the alleged trials mentioned in the '043 patent, or to refer to such trials as ongoing. Regardless of the rationale behind this omission, the omission stands of record. Unless the Examiner can cite to where these alleged Phase I and Phase II clinical trials are being conducted and by whom, the preponderance of evidence lies in favor of Applicants' contention that these trials were never conducted. Applicants again respectfully submit that a statement regarding non-existent clinical trials and non-existent data cannot properly serve as the Examiner's basis for rendering moot the issue of unpredictability in combination drug therapy.

With regard to the Examiner's comments regarding validity of the '043 patent, Applicants wish to make of record that they have not called into question its presumed validity. The claims of the '043 patent are indeed presumed to be valid. However, Applicants draw the Examiner's attention to the fact that the issued claims of the '043 patent are narrowly drawn to a method for

reducing residual $CD20^+$ tumor cells in bone marrow or stem cell tissue after myeloablative therapy in a subject in need of such treatment by administering an amount of a non-radiolabeled anti-CD20 antibody effective to reduce the number of residual $CD20^+$ tumor cells in the bone marrow or stem cell tissue (claim 1). The dependent claims recite the limitation that the subject had a B cell lymphoma (claim 5). The only issued claim drawn to additional combination therapy is claim 11, reciting the further administration of a chemotherapeutic agent to the subject that has undergone myeloblative therapy and therapy with the non-radiolabeled anti-CD20 antibody. Yet IL-2 is clearly identified as a "cytokine" in this patent, not a "chemotherapeutic agent." See the '043 patent at col. 3, lines 24-47. The "claims" of the corresponding WO publication that recite "[a] method of treating B-cell lymphoma comprising administering a synergistic therapeutic combination comprising at least one anti-CD20 antibody and at least one cytokine" (claim 12, and claims dependent therefrom) did not issue in the '043 patent. Applicants' comments of record calling into question whether the '043 patent includes an enabling disclosure to support claims drawn to a synergistic therapeutic combination of these two agents were directed to subject matter that has yet to be examined, and thus the patentability of this disclosed subject matter is yet to be determined.

In summary, Applicants respectfully submit that, at the very best, the '043 patent and its companion WO publication generically suggest combination therapy with anti-CD20 antibody and IL-2, leaving one of skill in the art with an invitation to experiment with many possible avenues of approach to try to achieve the desirable result, i.e., treatment of non-Hodgkin's lymphoma using this combination therapy. They do not provide enough guidance to form a reasonable expectation that the process as utilized by Applicants here would actually succeed. Where the prior art gives only general guidance as to the particular form of the invention or how to achieve it, as here, obviousness may not be found. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81, 90-91 (Fed. Cir. 1986). Accordingly, Applicants respectfully request reconsideration and withdrawal of this obviousness rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the rejection of the claims under 35 U.S.C. §103(a) is overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR §1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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